UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/016,604	12/07/2001	Pablo D. Garcia	PP016466.0002	6543

27476 7590 08/20/2009

NOVARTIS VACCINES AND DIAGNOSTICS INC.
INTELLECTUAL PROPERTY- X100B
P.O. BOX 8097
Emeryville, CA 94662-8097

EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	**PAPER NUMBER**
1648	

MAIL DATE	DELIVERY MODE
08/20/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/016,604	GARCIA ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77,78,80-84 and 114-116* is/are pending in the application.

4a) Of the above claim(s) *80-82* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77,78,83,84 and 114-116* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/7/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed 07 July 2009. Claims 1-76, 79 and 85-113 have been cancelled. Claims 114-116 have been added. Claims 77, 78, 80-84, and 114-116 are pending. Claims 80-82 are drawn to a nonelected subject matter and hence are withdrawn from further consideration pursuant to 37 CFR 1.142(b). Claims 77, 78, 83, 84, and 114-116 are currently examined.

Claim Objections

The objection to claim 14 is withdrawn in response to Applicant's amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

MAINTAINED REJECTION

The rejection of claims 77, 78, 83 and 84 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification commensurate in scope is maintained and extended to new claims 114-116 in response to Applicants' amendment.

Claims 77, 78, 83, 84 and 114-116 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for assaying, in a patient prostate sample, the RNA of HERV-K(CH) that is at least 150% relative to a control sample level, does not reasonably provide enablement for (a) assaying, in a patient prostate or blood sample, the polypeptide of HERV-K(CH) that is at least 150% relative to a control sample level; or (b) assaying, in a patient blood sample, the RNA of HERV-K(CH) that is at least 150% relative to a control sample level. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112, first paragraph, the courts have put forth a series of factors (MPEP §2164.01(a)). See, *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988); and *Ex Parte Forman*, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id*. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

The instant claims are directed to screening any part of the RNA of a human endogenous MMTV-like subgroup 2 (HML-2) retrovirus, HERV-K(CH) and detecting at

least 150% increased RNA level in a patient prostate or blood sample to determine the presence of prostate cancer.

The guidance in the specification is limited to detecting at least 150% more RNA of HERV-K(CH) in prostate cells only (page 24, line 23 to page 25, line 9; and page 74-75). However, the specification does not provide guidance on whether there is greater than 150% RNA level in blood samples. In other words, the specification only contains data for at least 150% elevated RNA level in prostate cells but not blood cells. Neither does the specification show whether the level of mRNA over-expression in one tissue type like prostate cells is correlated to the level of mRNA over-expression in blood. Furthermore, there is no evidence showing a tight correlation of RNA over-expression greater than 150% with prostate cancer in blood.

It is known in the art that HERV-K relative over-expression in peripheral blood mononuclear cells (PBMCs) or mononuclear cells from cord blood might be specifically associated with tumor development, but not specifically to one type of tumor. For instance, Depil *et al*. (2002) report a 500% to 1000% higher transcriptional activity or expression of HERV-K10-like *gag* gene in blood samples from leukemia patients, while Herbst *et al*.(1998) suggest detection of HERV-K gene products for diagnosing and monitoring germ cell tumors and trophoblastic disease, whereas Willer *et al*. (1997) report heterogenous expression pattern of HERV-K elements in human blood and solid tissues. Therefore, it is unpredictable whether an at least 150% relative higher expression of HERV-K RNA in blood is definitively indicative of prostate tumor but not

other types of carcinogenic diseases, such as breast cancer, gastric cancer or trophoblastic disease.

Furthermore, Applicants did not provided any clear-cut evidence that shows at least 150% higher than normal mRNA expression in the blood sample of only prostate cancer patients but not other patients. Given the high level of unpredictability in the art, it is uncertain whether prostate cancer can be preliminarily diagnosed or detected by the at least 150% elevated mRNA expression level in a blood sample alone.

The working example indicates at least 150% increased RNA expression in prostate tissue. However, the working example does not show a concordant RNA over-expression in a blood sample. Therefore, the instant specification and the working example do not address the vagueness of RNA over-expression in various cell types.

At the time the invention was made, no one has made a clear-cut showing of quantitative correlation between the RNA over-expression levels in various cell types. It is highly unpredictable whether the skilled artisan would observe the same 150% elevated RNA expression in blood samples as Applicants measured in the prostate tumor cells. Thus, the validity of the number, 150%, in the expression level of RNA in all cell types as an indication of prostate cancer remains questionable. Therefore, it would require undue and unpredictable experimentation for one skilled in the art to use the claimed method.

Applicants have not provided sufficient guidance to allow one skilled in the art to practice the claimed invention with a reasonable expectation of success and without undue experimentation. In the absence of such guidance and evidence, the

specification fails to provide an enabling disclosure. A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Response to Arguments

Applicant's arguments filed 07 July 09 have been fully considered but they are not persuasive. Applicants argue that, at the time of the claimed invention, it was well known in the art how to assay for RNA in blood samples. Applicants also argue that the Specification as filed disclosed that "'the up-regulation relative to the control (100%) will usually be at least 150%" without limiting the up-regulation to prostate cells only (page 25, line 17-19) and that the patient sample may be cells in blood or virions independent from prostate cells where the diagnostic method of the invention is based on HML 2 mRNA (page 2, line 27 to page 3, line 18). Applicants further argue that The Patent Office also offers no evidence or reasoning why it doubts Applicant's disclosure that blood cells can be used in the invention.

While Applicants correctly stated that it is well known in the art how to assay for RNA in blood samples, this is not the reason for the outstanding rejection on the lack of enablement of the claimed method. Although it is routine practice to screen for RNA level in blood samples, there is no teaching in the art that blood samples exclusively

from prostate tumor patients show at least 150% over-expression of HERV-K(Ch). Rather, there has been various reports of HERV-K over-expression associated with a variety of diseases such as breast tumors, germ cell tumors (Herbst, 1998), leukemia (Lepil, 2002), colon cancer, and high and low grade non-Hodgkin's disease (Willer, 1997), as set forth above in the analysis of the state and predictability of the art. Therefore, there is a high level of unpredictability in the correlation of HERV expression pattern with prostate cancer, especially since Huang *et al*. (2006) reported that tissue-specific expression of HERV is associated with multiple sclerosis, diabetes, autoimmune arthritis and that blood expression of HERV is associated with schizophrenia.

Even though Applicants correctly pointed out that the Specification as filed disclosed that "the up-regulation relative to the control (100%) will usually be at least 150%" and that “the patient sample is tissue sample, preferably, a prostate sample or a blood sample,” these simple statements do not provide sufficient guidance without a working example and any teaching in the art pertaining to HERV-K over-expression. In short, these statements in the specification at best only identify the claim elements in the instant invention. However, these statements cannot serve as objective evidence that unequivocally indicates a correlation of higher than 150% over-expression of HERV-K in blood samples with prostate cancer.

In response to Applicant’s argument that Examiner has presented no evidence to show that the present invention would not work for early detection of prostate cancer by assaying for at least 150% higher RNA expression level in patient blood sample, the

Examiner is not required to present evidence in making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112, first paragraph. MEPEP §2164.01. Examiner's analysis of the Wands factors and the articulation of reasoning provide the basis for Examiner's conclusion that the instant invention is not enabled by the disclosure as filed. Applicants have not provided sufficient guidance to allow one skilled in the art to practice the claimed invention with a reasonable expectation of success and without undue experimentation. In the absence of such guidance and evidence, the specification fails to provide an enabling disclosure. A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

In this case, Applicants have not addressed the issue of the lack of predictability in the art. HERV-K up-regulation has been shown in the blood sample of patients with disease of not only prostate tumor but also of breast tumors, testicular tumors, leukemia, etc. In summary, Applicants have not shown any correlation between 150% up-regulation of RNA expression in blood and prostate cancer. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). See M.P.E.P. §2164.03 [R-2]. Relationship of Predictability of the Art and the Enablement Requirement. Considering

the lack of data or relevant working examples in the specification, the broad scope of the claims, the complex state and nature of the art, and the teachings regarding unpredictability in this art, the Applicant has not provided sufficient information to enable those skilled in the art to make and use the full scope of the claimed invention without undue experimentation.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648

/Jeffrey S. Parkin/
Primary Examiner, Art Unit 1648

4 August 2009